DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
94752d

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

MAY 27 2004

Via Federal Express
WARNING LETTER

Michael J. Lipomi, Chair
Institutional Review Board Chair and
Chief, Executive Officer
Stanislaus Surgical Hospital
1421 Oakdale Road
Modesto, California 95355

Dear Mr. Lipomi:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of the Stanislaus Surgical Hospital Institutional Review Board (SSH IRB), which serves as the IRB for Stanislaus Surgical Hospital, and to request that prompt corrective actions be taken. Ms. Marie K. Kinkade and Mr. Thomas W. Gordon, investigators from FDA's San Francisco District Office conducted the inspection on December 16 through December 23, 2003. The purpose of the inspection was to determine whether your activities and procedures as an IRB complied with applicable FDA regulations. These regulations apply to certain clinical studies of products regulated by FDA.

You reviewed the following study at the request of the study's principal investigator: [redacted] study). The product under investigation in this study is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Our review of the establishment inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 56 – Institutional Review Boards and Part 812 – Investigational Device Exemptions. At the close of the inspection Ms. Kinkade and Mr. Gordon presented a Form FDA 483, "Inspectional Observations," to you for review and discussed the listed deviations. The deviations noted on the Form FDA 483 and our subsequent inspection report review are discussed below:

1. **Failure to have adequate IRB membership (21 CFR 56.107(a) and 56.107(d))**

   In accordance with 21 CFR 56.107(a) and 56.107(d), each IRB is required to have at least five members with varying backgrounds, be sufficiently qualified through experience, expertise, and diversity of the members, and have at least one member who is unaffiliated with the institution and not part of the immediate family of a person affiliated with the institution.

An example of your failure to satisfy this requirement includes, but is not limited to, the fact that your IRB was comprised of [redacted] members: you [redacted] Therefore, your IRB does not have the required minimum number of members, or a sufficient amount of experience, expertise, and diversity of membership as required by FDA regulations.

2. **Failure to have adequate written standard operating procedures (SOPs) governing the functions and operations of the IRB (21 CFR 56.108(a) & (b), 56.115(a)(6), and 21 CFR 812.66))**

According to FDA regulations, an IRB must prepare, maintain, and follow written procedures that describe the IRB functions and operations, including: conducting initial and continuing review of research; ensuring that changes to approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent hazards to human subjects; ensuring prompt reporting to the IRB, appropriate institution officials, and FDA of any unanticipated problems involving risks to human subjects or others and any instances of serious or continuing noncompliance with FDA regulations pertaining to IRBs or determinations of the IRB. (21 CFR 56.108(a), 56.108(b)) As part of its procedures for conducting initial review of research, the IRB should have procedures for determining whether each investigation presented for IRB approval involves a non-significant risk (NSR) or significant risk (SR) device. Except in limited circumstances, the SR/NSR determination must be made by the IRB before the sponsor may begin the investigation. (21 CFR 812.66) When developing and revising IRB procedures, you may find the FDA's guidance for Institutional Review Boards and Clinical Investigators, posted at http://www.fda.gov/oc/ohrt/irbs, to be a useful resource.

Examples of your failure to satisfy these requirements include, but are not limited to, the following:

Your IRB guidelines consisted of an undated document entitled [redacted] and a checklist which are used as the IRB procedures. This checklist and undated document are not adequate in that they lacked written procedures outlining the IRB's responsibilities for the following:

- Conducting initial and continuing review of research;

- Determining whether an investigation involves a significant risk (SR) or non-significant risk (NSR) device and which projects require review more than annually;

- Ensuring prompt reporting to your IRB, appropriate institutional officials and FDA of unanticipated problems involving risks to human subject or others, or any instance of serious or continuing noncompliance with FDA's IRB regulations or the requirements or determinations of your IRB; and

- Ensuring prompt reporting to your IRB of changes in research activity and progress reports by clinical investigators.

As part of your continuing review of research, IRB procedures should describe the reporting responsibilities and the information investigators should submit to the IRB in progress reports.

3. **Failure to provide adequate review of research and notify investigators in writing of decisions regarding approval or disapproval of research (21 CFR 56.109(a), 56.109(b), 56.109(e) and 56.109(f))**

The IRB is responsible for conducting initial and continuing review of research. Federal regulations require an IRB to conduct initial review of research proposals and continuing review of approved research, and to have authority to approve, require modifications in, or disapprove all research activities. (21 CFR 56.109(a) and 56.109(f)) An IRB is required to notify investigators in writing of its decision to approve or disapprove the proposed research activity or of modifications required to secure IRB approval. (21 CFR 56.109(e)) Also, in order to protect the rights and welfare of research subjects, an IRB must require that information given to subjects as part of informed consent includes the elements specified in 21 CFR 50.25 and must determine that informed consent will be sought in accordance with the requirements of 21 CFR Part 50. (21 CFR 56.109(b) & 56.111(a)(4))

Examples of your failure to satisfy these requirements include, but are not limited to, the following:

- On April 23, 2003, the IRB retroactively approved informed consent forms dated [redacted] and [redacted] and granted blanket approval of subsequent revisions to the forms.

- The informed consent forms for the [redacted] study do not contain all required elements, such as the purpose of the study and contact information for questions related to research subjects' rights and research-related injuries.

- Records reviewed for the [redacted] study revealed no IRB discussion of and no record of correspondence with the investigator regarding approval o[redacted] [redacted] modification that the sponsor requested in its [redacted] letter to the IRB.

We also note that your IRB received all documents regarding the [redacted] study, including revisions, from [redacted] the study sponsor. While FDA recognizes that direct communication between an IRB and a study sponsor is essential, the IRB should also establish direct communication with the clinical investigators as well.

4. **Failure to prepare and maintain adequate documentation of IRB activities (21 CFR 56.115(a)(1), 56.115(a)(2), 56.115(a)(3), 56.115(a)(4) and 56.115(b))**

   FDA regulations require that an IRB prepare and maintain adequate documentation of its activities, including: copies of all research proposals reviewed; approved sample consent documents; records related to continuing review and approval; IRB meeting minutes in sufficient detail to show actions taken by the IRB; votes on these actions including how members voted; a written summary of the discussion of controverted issues and their resolution; and copies of all correspondence between the IRB and the investigators. (21 CFR 56.115(a)) These records must be retained for at least 3 years after completion of the research. (21 CFR 56.115(b))

   Examples of your failure to satisfy recordkeeping requirements include but are not limited to the following:

   - Your letter dated [redacted] for extending the approval of the [redacted] study, was missing information concerning what was approved. The letter stated, "Your compliance with the approval on the following: *[blank space]*." It could not be determined what the IRB approved during continuing review and if the referenced document or item was attached to the letter.

   - Your IRB meeting minutes did not include required information. For example, minutes of meetings held on April 10, 2003, April 23, 2003, June 26, 2003, and October 9, 2003 were not written in sufficient detail to describe what the members reviewed and approved at these meetings. Various meeting minutes lacked other information, such as: IRB actions considered after the sponsor's cancellation of the research, after the clinical investigator's failure to promptly report unanticipated problems and study protocol deviations, and due to a missing report from a clinical investigator. All meeting minutes failed to identify the number of members voting for, against, and abstaining from voting for IRB actions.

   - Your approval letter, dated [redacted] for the [redacted] study mentioned that the following were submitted to you by the clinical investigator: a progress report and assessment of risks, benefits, and the appropriateness of the approved informed consent form. However, this correspondence submitted by the clinical investigator could not be found at your IRB during the inspection.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As an IRB, it is your responsibility to ensure that investigations are conducted in accordance with applicable FDA regulations.

Within fifteen (15) days, you must respond to this letter in writing. You should be aware that FDA considers the IRB actions to be serious violations of the law. Failure to respond to this letter and to take prompt action to correct these violations may result in further regulatory action, including initiation of procedures to disqualify the IRB.

Please address your correspondence to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Linda Godfrey, Consumer Safety Officer.

A copy of this letter has been sent to FDA's San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, California 94502. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Linda Godfrey at (301) 594-4723 extension 134.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health